IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Daniel E. AFAR, *et al.*

Serial No.: 09/323,597

Filing Date: June 1, 1999

For: NOVEL TUMOR ANTIGEN USEFUL IN DIAGNOSIS AND THERAPY OF PROSTATE AND COLON CANCER

Examiner: Gary B. NICKOL, Ph.D.

Group Art Unit: 1642

DECLARATION OF ARTHUR B. RAITANO, Ph.D. UNDER 37 C.F.R. § 1.132

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Arthur B. Raitano, Ph.D., declare as follows:

1. I am a named inventor on United States Patent Application No. 09/323,597, the patent application identified above.

2. I am a Research Scientist III at Agensys, Inc., the assignee of the entire right and interest in the patent application identified above. I hold a B.S. degree in biology from the

University of California, Davis, and a Ph.D. in Microbiology and Immunology from the University of Arizona, Tucson. I have approximately 18 years of experience in cellular and molecular immunology. My experience includes five years of graduate research, and seven years of post-doctoral research including the raising and use of antibodies to study signal transduction pathways in human cancers. I have 7 years of experience at Agensys in the generation and characterization of antibodies to novel cancer-associated antigens. I have authored 17 journal articles in the field of molecular biology and immunology. I have attached a copy of my current CV as Exhibit A.

3. I have reviewed the specification of the patent application identified above. I have also reviewed the pending independent claim (claim 72) of this application, which reads as follows:

> 72. A method for inhibiting the growth, viability and/or survivability of cancer cells that express the nucleotide sequence SEQ. ID. No.: 1 or the cDNA in ATCC deposit 207097 (20P1F12/TMPRSS2), the method comprising:
>
> administering to the cancer cells an antibody or fragment thereof that specifically binds to a 20P1F12/TMPRSS2 protein, thereby inhibiting the growth, viability and/or survivability of said cancer cells.

4. It is my understanding that this claim is being rejected by the United States Patent and Trademark Office on the basis that the specification does not enable a person of ordinary skill in the art to practice the invention of claim 72, that is, to make and use the invention as claimed. Specifically, I understand that this rejection is due to the lack of predictability that administration of an antibody, or fragment thereof, that specifically binds to a 20P1F12/TMPRSS2 protein would indeed inhibit the growth, viability or survivability of cancer cells.

5. We have conducted experiments demonstrating the effect of an anti-TMPRSS2 monoclonal antibody (Mab) designated M9-5.1 on the growth of LNCaP prostate cancer cells. Anti-keyhole limpet hemocyanin (anti-KLH) antibodies were used as controls for these

experiments. The data is presented in Exhibit B and Exhibit C which accompany this declaration.

6. Exhibit B shows the effect of the anti-TMPRSS2 monoclonal antibody M9-5.1 MAb on LNCaP prostate cancer cell growth at two different concentrations. At a concentration of 40 ug/ml, M9-5.1 MAb demonstrated an inhibitory effect on LNCaP cell growth as compared to anti-KLH MAb at the same concentration.

7. Exhibit C shows the effect of using the anti-TMPRSS2 antibody in conjunction with a second antibody which binds to the first antibody (goat anti-mouse IgG-toxin), where the second antibody has a toxin conjugated to it (the toxin is saporin, a ribosome-inactivating protein). The effects of this treatment are even more significant. The anti-TMPRSS2 M9-5.1 antibody/anti-mouse IgG-saporin treatment showed more inhibitory effect than the anti-KLH antibody/anti-mouse IgG-saporin control down to 1.6 ng/ml of antibody complex.

8. It is clear from the data presented in Exhibits B and C that "administering to the cancer cells an antibody or fragment thereof that specifically binds to a 20P1F12/TMPRSS2 protein" results in "inhibiting the growth, viability and/or survivability of said cancer cells," as the claim language states.

9. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Executed this 11 day of October, 2004, at Santa Monica, California.

Arthur B. Raitano, Ph.D.

EXHIBIT A

CURRICULUM VITAE

Arthur Bartholomew Raitano

Agensys, Inc. Santa Monica, California

Education:

Bachelor of Science, Biology	1984	University of California at Davis Davis, California
Doctor of Philosophy, Microbiology and Immunology	1991	University of Arizona, Tucson, Arizona

Experience:

1983-1985	Hospital Operating Room Assistant II, University of California, Davis, Medical Center.
1986-1987	Graduate Research Assistant II, Dept. of Microbiology and Immunology, University of Arizona. Advisor: Dr. Murray Korc.
1990-1991	Postgraduate Researcher, with Dr. Murray Korc Dept. of Medicine, University of California, Irvine.
1991-1993	Postdoctoral Fellow, with Dr. B.J. Wisnieski, Dept. of Microbiol. and Molec. Genetics, University of California, Los Angeles.
1993-1996	Postdoctoral Fellow, with Dr. Charles Sawyers, Dept. of Medicine, Div. of Hematology and Oncology, University of California, Los Angeles.
1996-1997	Assistant Researcher, with Dr. Charles Sawyers, Dept. of Medicine, Div. of Hematology and Oncology, University of California, Los Angeles.
1997-1998	Staff Scientist, UroGenesys, Inc., Santa Monica, California.
1998-2001	Research Scientist I, UroGenesys/Agensys, Inc. Santa Monica, California
2001-2003	Research Scientist II, Group Leader Protein Expression, Agensys, Inc. Santa,Monica, California
2003-present	Research Scientist III, Group Leader Protein Expression, Agensys, Inc. Santa Monica, California

Fellowship Awards Received:

- NIH Predoctoral Trainee, University of Arizona Cancer Biology Training Grant Program, 1986-1990.
- NIH Postdoctoral Trainee, UCLA Atherosclerosis Training Grant Program, 1991-1993.
- NIH Postdoctoral Trainee, UCLA Tumor Cell Biology Training Grant Program, 1993-1994.

- Jaye Haddad/Concern Foundation Fellowship in Tumor Immunology, 1994.
- UCLA Jonsson Comprehensive Cancer Foundation Fellowship, 1994-1995.

Publications:

1. Scuderi, P., K.E. Sterling, **A.B. Raitano**, T.M. Grogan and R.A. Rippe. 1987. Recombinant interferon gamma stimulates the production of human tumor necrosis factor *in vitro*. J. Interferon Res. 7:155-164.

2. Scuderi, P., R.A., Rippe, **A.B. Raitano** and J. Rybski. 1989. Human sera and culture supernatants from human tumors and diploid fetal fibroblasts suppress tumor necrosis factor secretion *in vitro*. J. Leuk. Biol. 46:34-40.

3. Scuderi, P., R.T. Dorr, J.P. Liddil, P.R. Finley, T. Meltzer, **A.B. Raitano** and J. Rybski. 1989. Alpha-globulins suppress human leukocyte secretion of tumor necrosis factor. Eur. J. of Immunol. 19:939-942.

4. **Raitano, A.B.**, P. Scuderi and M. Korc. 1990. Binding and biological effects of tumor necrosis factor and gamma interferon in human pancreatic carcinoma cells. Pancreas 5:267-277.

5. **Raitano, A.B.**, P. Scuderi and M. Korc. 1990. Long term effects of tumor necrosis factor and gamma interferon in human pancreatic carcinoma cells. Int. J. of Pancreatology 6:109-118.

6. **Raitano, A.B.** and M. Korc. 1990. Tumor necrosis factor upregulates gamma interferon binding in a human carcinoma cell line. J. Biol. Chem. 265:10466-10472.

7. **Raitano, A.B.**, P. Scuderi and M. Korc. 1991. Upregulation of gamma interferon binding by tumor necrosis factor and lymphotoxin: disparate potencies of the cytokines and modulation of their effects by phorbol ester. J. Interferon Res. 11:61-67.

8. **Raitano, A.B.** and M. Korc. 1993. Growth inhibition of a human colorectal carcinoma cell line by IL-1 is associated with enhanced expression of IFN-Y receptors. Cancer Res. 53:636-640.

9. **Raitano, A.B.**, J. Halpern, T.M. Hambuch, and C.L. Sawyers. 1995. The Bcr-Abl leukemia oncogene activates Jun kinase and requires Jun for transformation. Proc. Natl. Acad. Sci. 92:11746-11750.

10. Dickens, M., J. Rogers, J. Cavanagh, **A. Raitano**, Z. Xia, J. R. Halpern, M. E. Greenberg, C. Sawyers and R.J. Davis. 1997. A cytoplasmic inhibitor of the JNK signal transduction pathway. Science, 277:693-696.

11. **Raitano, A.B.**, Y. Whang and C.L. Sawyers. 1997. Signal transduction by wild-type and leukemogenic Abl proteins. Biochem. Biophys. Et. Acta, 1333:F201:216.

12. Xu FH, Sharma S, Gardner A, Tu Y, **Raitano A**, Sawyers C, and Lichtenstein A. 1998. Interleukin-6-induced inhibition of multiple myeloma cell apoptosis: support for the hypothesis that protection is mediated via inhibition of the JNK/SAPK pathway. Blood. 92:241-251.

13. Hubert RS, Vivanco I, Chen E, Rastegar S, Leong K, Mitchell SC, Madraswala R, Zhou Y, Kuo J, **Raitano AB**, Jakobovits A, Saffran DC, and Afar DE. 1999. STEAP: a prostate-specific cell-surface antigen highly expressed in human prostate tumors. Proc Natl Acad Sci U S A. 96:14523-14528.

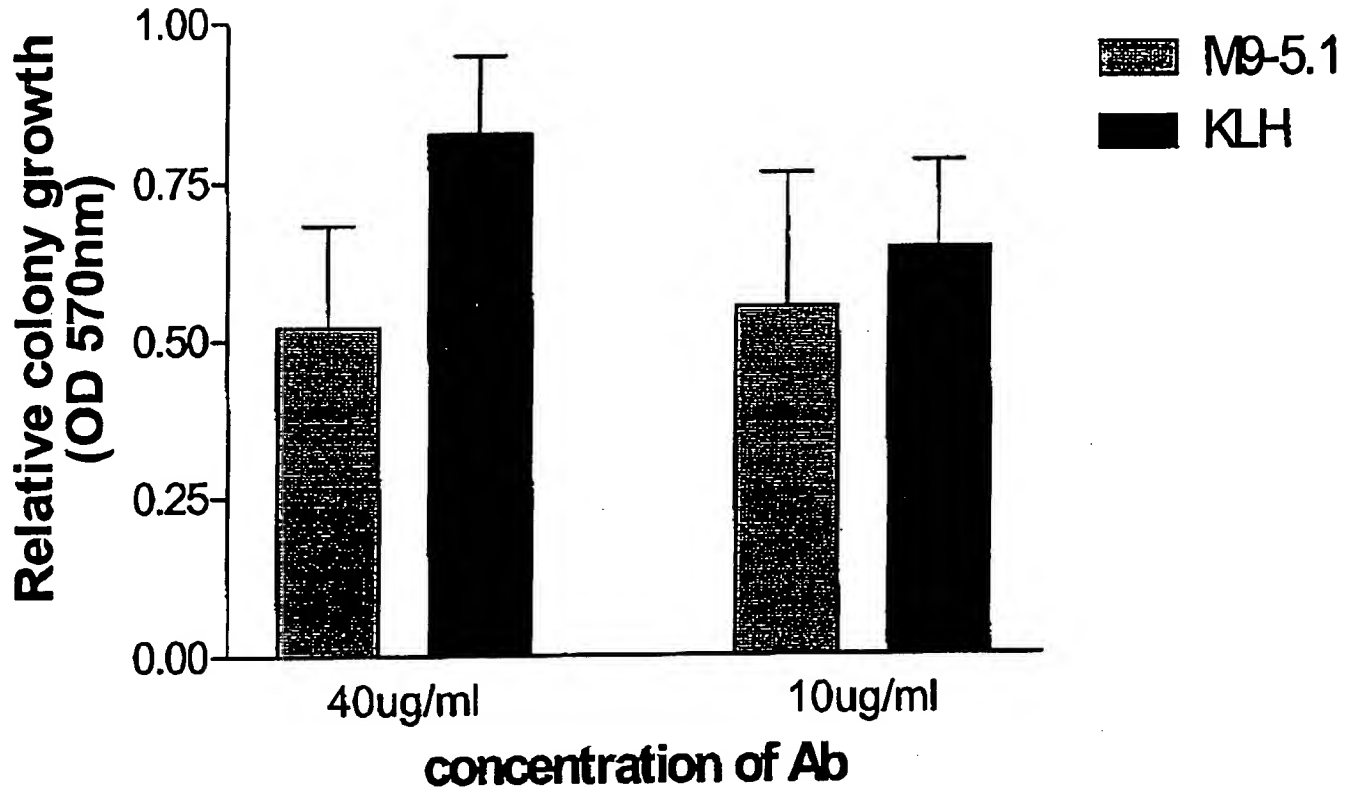
14. Neshat MS, **Raitano AB**, Wang HG, Reed JC, and Sawyers CL. 2000. The survival function of the Bcr-Abl oncogene is mediated by Bad-dependent and -independent pathways: roles for phosphatidylinositol 3-kinase and Raf. Mol Cell Biol. 20:1179-1186.

15. Gu Z, Thomas G, Yamashiro J, Shintaku IP, Dorey F, **Raitano A**, Witte ON, Said JW, Loda M, and Reiter RE. 2000. Prostate stem cell antigen (PSCA) expression increases with high gleason score, advanced stage and bone metastasis in prostate cancer. Oncogene. 2000 Mar 2;19(10):1288-1296.

16. Saffran DC, **Raitano AB**, Hubert RS, Witte ON, Reiter RE, and Jakobovits A. 2001. Anti-PSCA mAbs inhibit tumor growth and metastasis formation and prolong the survival of mice bearing human prostate cancer xenografts. Proc Natl Acad Sci U S A. 98:2658-2663.

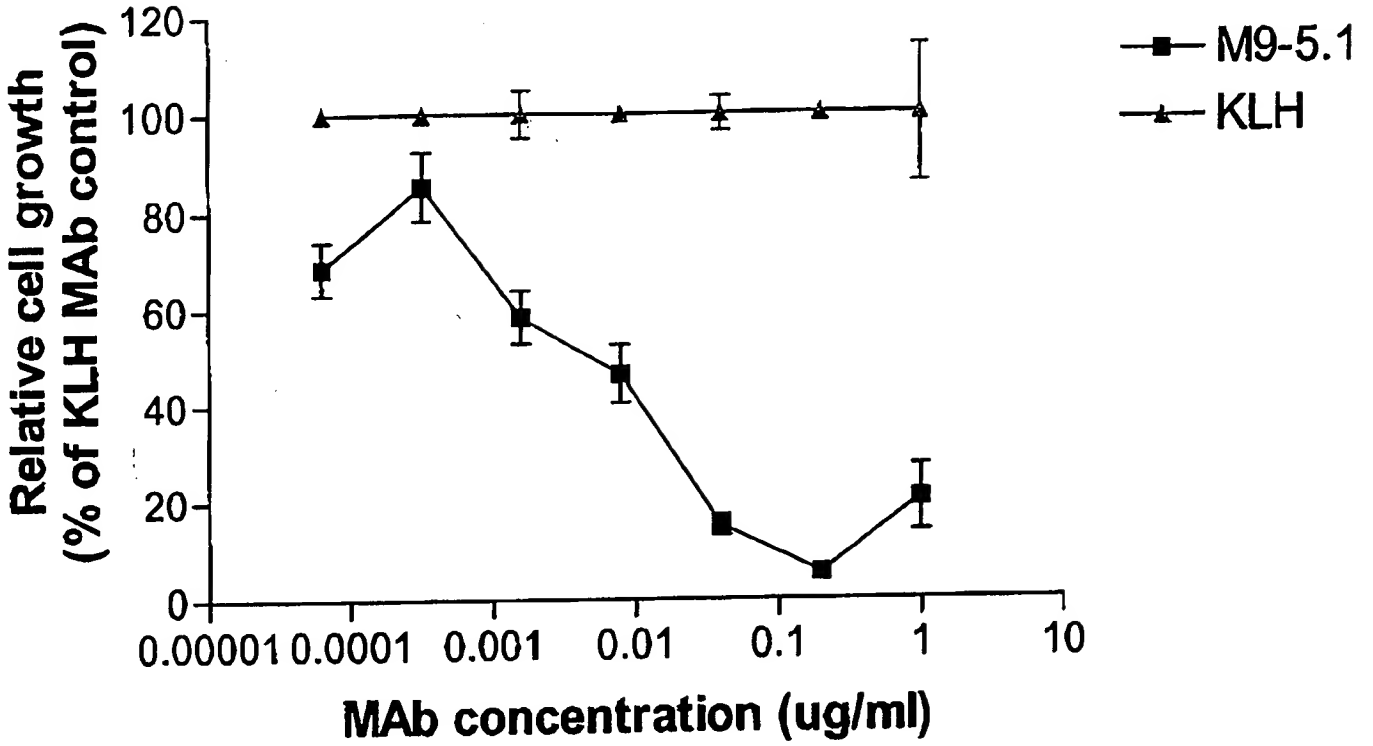
17. Afar DE, Vivanco I, Hubert RS, Kuo J, Chen E, Saffran DC, **Raitano AB**, Jakobovits A. 2001. Catalytic cleavage of the androgen-regulated TMPRSS2 protease results in its secretion by prostate and prostate cancer epithelia. Cancer Res. 61:1686-1692.

Exhibit B: Effect of anti-TMPRSS2 MAb M9-5.1 on LNCaP prostate cancer cell colony growth



300 LNCaP cells were plated in the presence of the indicated concentrations of either MAb M9-5.1 or control KLH MAb and allowed to adhere and form colonies in a 24 well plate. Relative colony growth was determined by crystal violet staining and quantitated by measuring the optical densities of the eluted dye.

Exhibit C: Inhibition of LNCaP prostate cancer cell growth with anti-TMPRSS2 MAb M9-5.1 bound with toxin-conjugated secondary antibody



LNCaP cells (4000 cells/well) were incubated for 72 hours with the indicated amount of either MAb M9-5.1 or control KLH MAb in the presence of a 3 fold excess of goat anti-mouse IgG-toxin (saporin) conjugated secondary Ab. Relative proliferation was determined by 3H-thymidine incorporation. Data are the means ± SD of triplicate determinations and are expressed as % growth compared to the KLH control MAb.